

VESPA: A New, Fast Approach to Electrostatic Potential-Derived Atomic Charges from Semiempirical Methods

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ABSTRACT: An improved semiempirical method for computing electrostatic potential-derived atomic charges is described. It includes a very fast algorithm for the generation of the grid points around the molecule and the calculation of the electrostatic potential at these points. The dependency of the atomic point charges obtained on the number of grid points used in the fitting procedure is examined. For "buried" atoms a high density grid is necessary. It is possible to obtain 6-31G*-quality atom-centered point charges, even for phosphorus compounds, using AM1 or PM3. This approach can therefore be recommended for general use in QSAR or molecular mechanics for any organic and bioorganic system up to about 200 atoms. © 1997 by John Wiley & Sons, Inc. *J Comput Chem* 18: 744–756, 1997

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Introduction

Non-bonded interactions between molecules are due to a large extent to the static distribution of electron density in the interacting species. Complimentary distributions of charge result in favorable Coulombic interactions. These long range

interactions are particularly important in molecular recognition processes in biology, e.g. ligand-receptor interactions.^{1–5} Experimentally, the electron density distribution in molecules may be observed e.g. using deformation density calculations from X-ray crystallography or ESCA. Theoretically, the electron density is described by the computed wavefunction over all space. However, it is often convenient (in QSAR applications for example) to assign electron density to atoms. Atom-centered charges are of course a gross approximation but it is possible to reproduce important molecular prop-

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erties (e.g. dipole moments) reliably using them. The assignment of useful net atomic charges has been attempted with many different algorithms. The simplest is to use the electronegativity of the atoms.^{6a,b} However, conjugation and polarizability effects suggest that quantum mechanically derived charges may be more reliable in more complex systems. The simplest approximation to the charge density is obtained from the main diagonal of the density matrix (Coulson).⁷ However, this does not take into account the anisotropic partitioning of atomic charge between bonded atoms. A modification of this approach including the overlap matrix elements in the calculation, due to Mulliken⁸, has been used extensively in deriving QSARs. A further step forward is the distributed multipole analysis.⁹ Partitioning the atomic charge is the major problem in calculating excess atomic charges from the density matrix. Many different methods of partitioning the charges have been formulated. However, they are all somewhat arbitrary. A more useful approach to describing the electronic distribution in molecules may be to choose an atom-centered charge distribution that reproduces molecular properties at and outside a surface (usually the van der Waals' surface) appropriate to the range of distances at which molecules interact.¹⁰ One such useful property is the electrostatic potential, which describes the forces exerted on a positive probe of unitary charge at the desired surface. Complementarity between electrostatic interactions in molecules is also seen in their electrostatic potential distributions.¹¹ There are various methods of deriving potential-based charges using *ab initio* and semiempirical techniques. Most differ in the way they generate the grid points for the fitting procedure. Chirlian and Francl (CHELP)¹² use spherical shells, 1 Å apart, of fourteen nearly symmetrically placed points around each atom. Points within the van der Waals' radius of any of the atoms and those more than 3 Å outside the vdW surface of the molecule are discarded. Breneman and Wiberg (CHELPG)¹³ defined a cube of points spaced 0.3–0.8 Å apart containing the molecule and including 2.8 Å of headspace on all sides. Besler, Merz and Kollman¹⁴ (MK) use the Connolly molecular surface algorithm to define points on several concentric shells (1.4, 1.6, 1.8 and 2.0 times the vdW radius) surrounding the molecule. Most of the semiempirical methods use modified *ab initio* algorithms. See, for example Ferenczy and coworkers¹⁵ for a modified CHELP procedure or Orozco and Lueg¹⁶ for a variation of the MK method.

In the present article we describe Vamp Electro-Static Potential-Derived Atomic Charges (VESPA), a new approach for deriving high quality ESP charges using the three semiempirical methods MNDO¹⁷, PM3¹⁸ and AM1.¹⁹ The discussion of our results is divided into two sections: the dependency of the ESP-derived point charges on the number of grid points used during the fitting procedure, especially for buried atoms, and the quality of the semiempirically derived atomic charges compared to *ab initio* HF/6-31G* values.

Computational Methods

The charge-fitting process begins with the calculation of the electrostatic potential for each point in a grid around the molecule. The points were generated using a modified Marsili algorithm^{20,21} with variable step size (edge length), which enables us to control the number of the grid points. All points within 1.4 times the van der Waals' radius of the molecule were eliminated, the maximum distance of the grid points is twice the vdW radius plus the step size.

Figure 1 shows such a grid produced by VESPA for the tetramethylammonium ion using a step size of 0.3 Å. Figure 2 shows how the number of grid points changes with the chosen step size (Å) for the same ion. In this plot the step size varies from 5.7 Å to 0.3 Å. In our final version it is possible to choose values between 1.0 Å and 0.20 Å.

The electrostatic potential at these points is then calculated using the NAO-PC model²² included in the semiempirical software package VAMP5.5.²³ The ESP in general is given by

$$V(r) = \sum_{\alpha} \frac{Z_{\alpha}}{|R_{\alpha} - r|} - \int \frac{\rho(r') dr'}{|r' - r|}, \quad (1)$$

where $V(r)$ electrostatic potential at any point r

Z_{α} charge of atom α located at R_{α}

$\rho(r')$ electronic density function of the molecule

Within the monopole approximation equation (1) simplifies to

$$V_i = \sum_{j=1}^n \frac{q_j}{r_{ij}}, \quad (2)$$

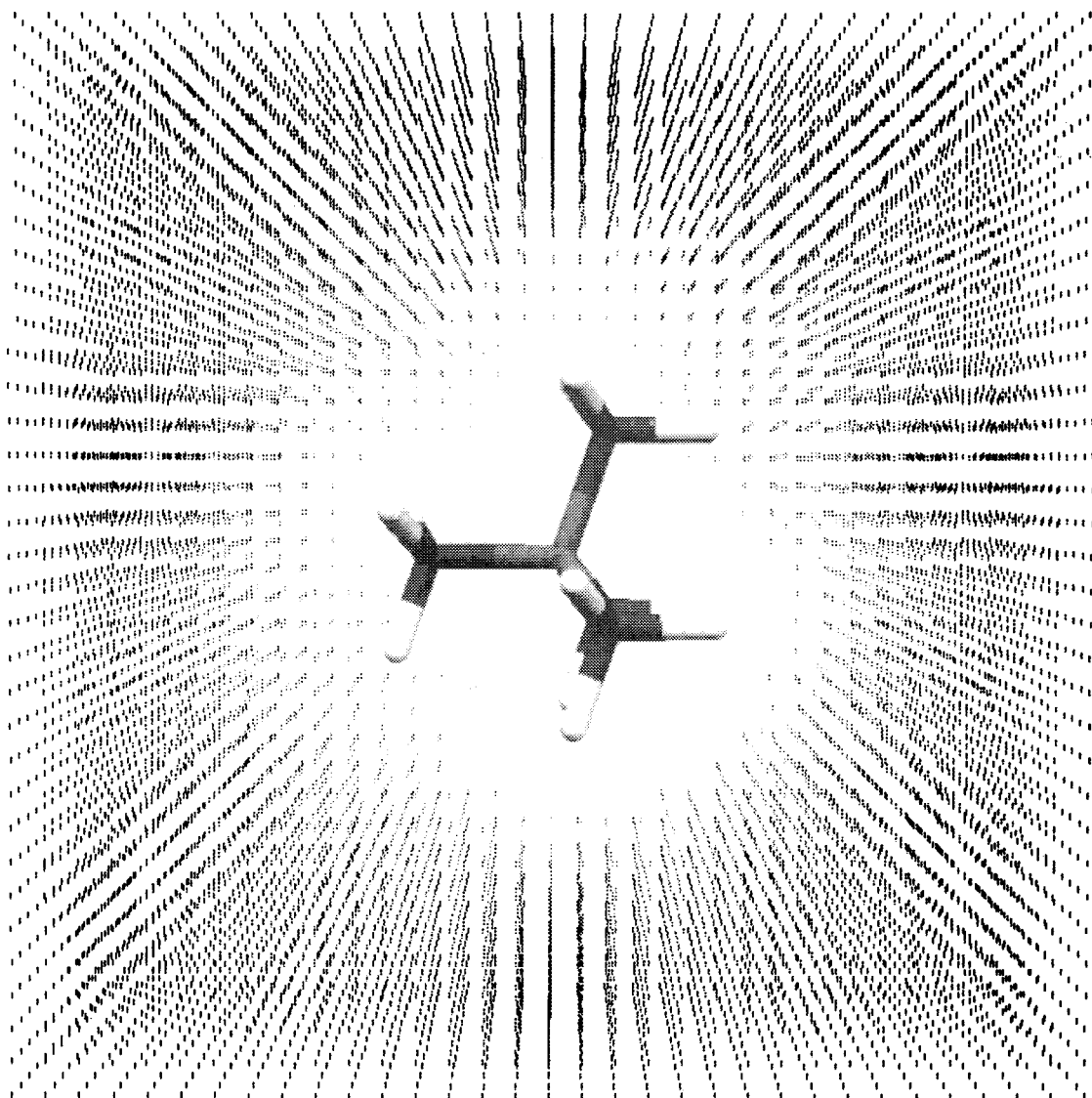


FIGURE 1. Tetramethylammonium ion surrounded by a grid of points generated with VESPA. Several layers have been removed in order to show the cavity.

where n number of atoms
 q_j atomic point charge
 r_{ij} distance between atom j and grid point i

Using the NAO-PC model, where the charge distribution of each heavy atom is represented by nine point charges (including the core charge) equation (1) becomes

$$V(\mathbf{r}) = \sum_{\alpha(\alpha \notin H)} \sum_{i=1}^{2n_{\text{orb}}+1} \frac{q_{i\alpha}}{|\mathbf{r}_{i\alpha} - 8hr|} + \sum_{\alpha(\alpha \in H)} \frac{q_{\alpha}}{|\mathbf{R}_{\alpha} - \mathbf{r}|}, \quad (3)$$

where $q_{i\alpha}$ charge of the NAO-PCs located at $r_{i\alpha}$
 q_{α} charge from the hydrogen atoms located at r_{α}

The double sum gives the contribution of the heavy atoms to the electrostatic potential, and the second term treats the hydrogen atoms.

This enables us to construct a very fast algorithm for the calculation of ESP-derived atomic charges, in which the most time consuming step is the final linear least squares fit procedure suggested by Chrilian and Francl.¹² It avoids disadvantages of nonlinear least squares fit procedures such as the need for initial guess charges, iterative

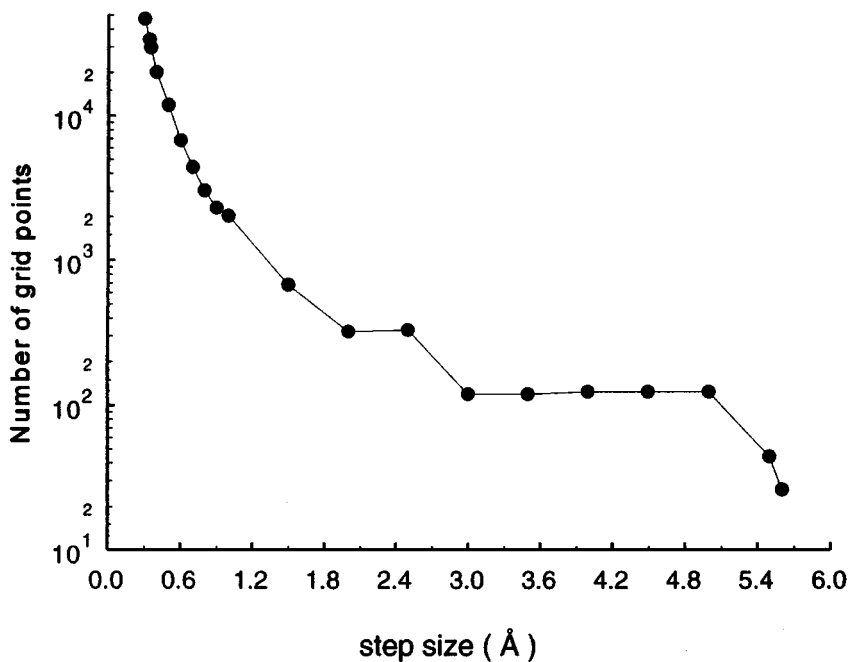


FIGURE 2. Dependence of the number of generated grid points on the step size (Å) in the “Marsili” algorithm.

solution procedures and possible convergence problems. The only constraint used is that the sum of the atomic charges match the actual molecular charge.

Most of the 6-31G* ESP atomic charges are taken from Besler, Merz and Kollman.¹⁴ The ESP charges for the phosphorus compounds are calculated using the MK¹⁴ procedure using GAUSSIAN 92.²⁴ All semiempirical calculations were performed on an Indigo² (R44000, 200 MHz), and all *ab initio* calculations on an HP 735 workstation (99 MHz).

Results and Discussion

DEPENDENCE ON THE NUMBER OF GRID POINTS

As mentioned above, we first tested the dependency of the calculated ESP atomic charges on the number of grid points used in the fitting procedure. Woods and coworkers²⁵ found that, especially for buried atoms, problems may occur if the number of points is too low. They found that about 1000 points per atom are needed to obtain a well defined atomic charge on the C atom of

methanol using a modified CHELP algorithm and the experimental geometry. The representation of the electrostatic potential near this atom is otherwise poor.

On the other hand, Francel et al.²⁶ have shown that the last squares matrix for this fitting problem may be rank deficient and that statistically valid charges cannot always be assigned to all atoms in a molecule. This problem increases with the size of the molecule. They conclude that increasing the point density has no or little influence on the quality of the point charges obtained.

We therefore decided to use two test systems to investigate the effect of increasing point density on the quality of the resulting atomic charges for our VESPA algorithm. The tetramethylammonium ion with 4 buried carbon atoms and a completely buried nitrogen is the first test case. The resulting atomic charges for different step sizes (number of points) are shown in figure 3.

The corresponding computational times and some additional information are given in table I. As expected, the charge calculated for the nitrogen atom changes significantly for small numbers of grid points.

The changes for the C point charge are smaller but also not negligible. Starting at about 12000

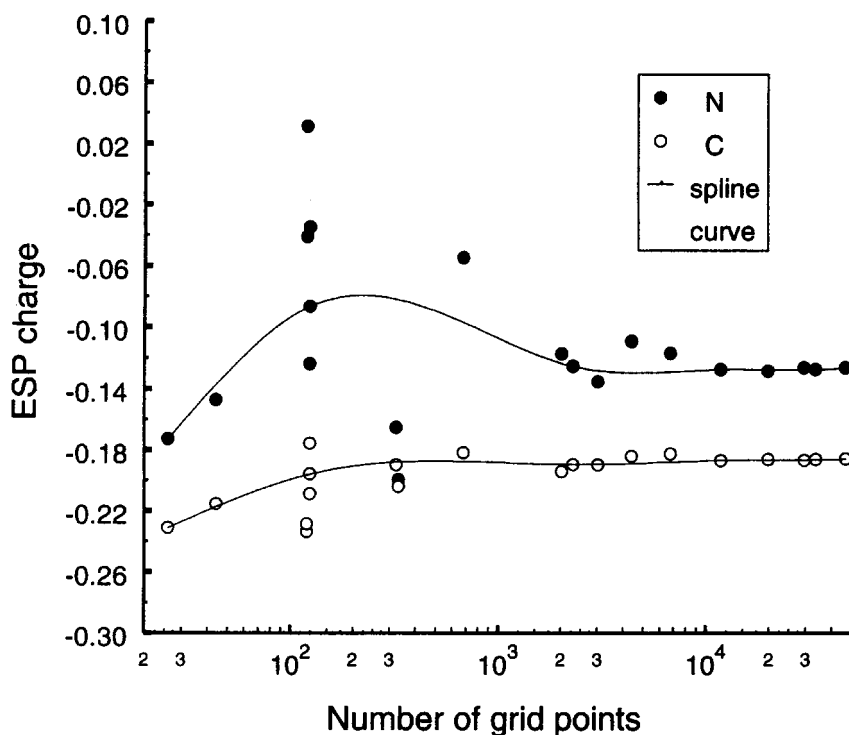


FIGURE 3. Dependence of the ESP-derived atomic charges (electronic charges) for the nitrogen and one carbon atom in the tetramethylammonium ion on the number of grid points used in the charge fitting procedure.

TABLE I.
Results for the Test Calculations on Tetramethyl-
Ammonium Ion (electronic charges).

Step size (Å)	Number of points	Charge on C	Charge on N	Calculation Time (s)
5.6	26	-0.231	-0.173	0.06
5.5	44	-0.216	-0.148	0.07
5.0	124	-0.209	-0.124	0.09
4.5	124	-0.196	-0.087	0.13
4.0	124	-0.176	-0.035	0.21
3.5	120	-0.234	-0.041	0.19
3.0	120	-0.229	0.031	0.22
2.5	331	-0.204	-0.120	0.30
2.0	322	-0.190	-0.166	0.31
1.5	678	-0.182	-0.055	0.53
1.0	2023	-0.194	-0.117	0.64
0.9	2297	-0.190	-0.125	0.73
0.8	3028	-0.190	-0.136	1.13
0.7	4410	-0.184	-0.109	1.37
0.6	6782	-0.183	-0.117	2.08
0.5	11841	-0.187	-0.128	3.64
0.4	19966	-0.187	-0.128	6.06
0.35	29667	-0.187	-0.127	9.10
0.34	33650	-0.186	-0.128	11.11
0.3	46903	-0.187	-0.127	14.36

points (0.5 Å step size) the calculated point charges at both atoms converge.

The octapeptide angiotensin II (146 atoms) was chosen as the second test system. The resulting atomic charges have already been published.²⁷ In figure 4 they are compared with those assigned by the AMBER²⁸ force field. In most parts of the molecule there is a good agreement between the two methods. For a detailed discussion see reference 27. The most important point here is that a step size of 0.3 Å (291,647 points) or smaller is necessary for this system, otherwise some of the point charges obtained have no chemical relevance.

On the basis of these results we conclude that using a very high density of potential points can improve the potential derived charges obtained for large molecules. The Ala₂₈ α-helix reported in reference 27 demonstrates, however, that increasing the number of points is not always the solution, as shown by Franci et al.²⁶ The present work does however, show that a very high density of points does improve the situation, although the CHELP SVD²⁶ procedure represents less of a "brute force" approach.

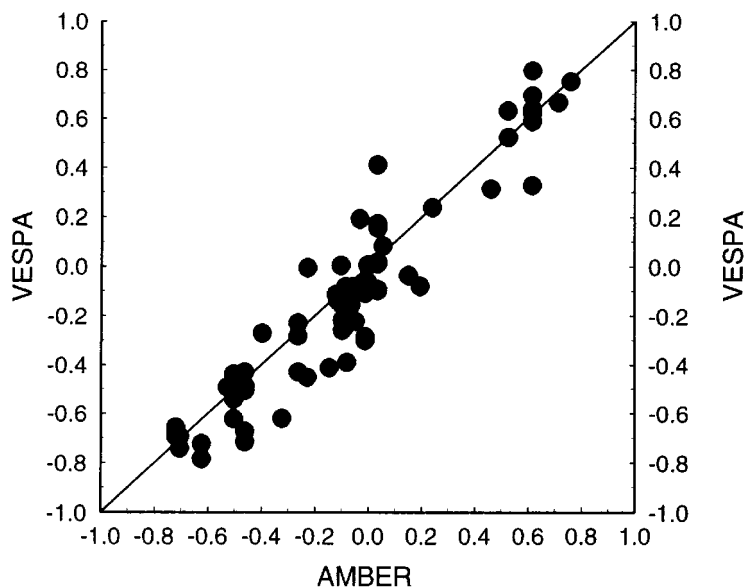


FIGURE 4. Plot of AMBER assigned atomic charges against VESPA derived point charges for angiotensin II (only for heavy atoms).

COMPARISON WITH *AB INITIO* DATA

For the comparison of our ESP charges with 6-31G* values we chose the 0.5 Å step size as a good compromise between accuracy of the derived point charges and computational time.

In order to be able to compare our results with HF/6-31G* data, we have used the same 20 test structures as Besler, Merz and Kollman¹⁴ plus 7 phosphorus compounds. The results are given in table II. The semiempirical RRMS (relative root mean square) deviations of the fitted molecular electrostatic potentials (MEPs) are of the same magnitude as the corresponding *ab initio* values. The semiempirical charges are generally smaller than the 6-31G* ones, but agree very well in sign and relative magnitude.

We have also compared AM1, PM3 and MNDO potential-derived charges with *ab initio* results and correlated the charges determined directly from the appropriate wavefunction using the method described by Pople and Beveridge²⁹ ("Coulson" method) with 6-31G* ESP charges. These results are summarized in table III.

AM1 ESP charges correlate with the 6-31G* ESP charges with $R = 0.934$ and a standard deviation of 0.108. This is shown in figure 5.

If we omit the phosphorus compounds, the correlation coefficient increases to 0.954 (standard deviation of 0.104). Without the P- and S-compounds

the correlation coefficient reaches 0.960 (0.098). For PM3 the corresponding correlation coefficients vary between 0.896 and 0.940, with standard deviations of 0.140 and 0.134, respectively. Figure 6 shows the plot including the whole data set.

For MNDO the resulting correlation coefficients are between 0.80 (Std. dev. 0.177) and 0.888 (Std. dev. 0.176).

Thus, from this data set we find that AM1 is best for reproducing 6-31G* (MK) ESP charges. PM3 also gives good results, especially without the P-compounds, whereas MNDO does not perform as well. Thiel³⁰ has introduced a parametrized MNDO-based technique to cure this problem.

For the P-compounds we also used the CHELPG method¹³ instead of MK to obtain the 6-31G* values. The resulting correlation coefficients between these charges and the VESPA charges are in the same range as those described above.

Kollman and coworkers³¹ have described the RESP method, designed to improve the quality of the ESP charges. They use a restraint in the form of a hyperbolic penalty function in the charge fitting procedure. This requires an iterative solution to self consistency in q_j (the point charge at atom j). We tried a similar approach for our VESPA algorithm, but achieved no real improvement. In some cases, especially during the test calculation for the tetramethylammonium ion, we experienced major

TABLE II.
Calculated AM1, PM3, MNDO, and 6-31G* Electrostatic Potential-Derived Charges (electronic charges).

Molecule ^a	Method ^b			
	AM1	PM3	MNDO	6-31G*
Ammonia				
N	−1.129	−0.897	−0.909	−1.091
H	0.376	0.299	0.303	0.363
RRMS ^c	0.106	0.157	0.109	0.135
Methane				
C	−0.264	−0.111	0.074	−0.490
H	0.066	0.028	−0.019	0.123
RRMS	0.323	0.515	0.655	
Acetylene				
C	−0.152	−0.129	−0.115	−0.298
H	0.152	0.129	0.115	0.298
RRMS	0.064	0.069	0.063	0.053
Ethylene				
C	−0.159	−0.132	−0.104	−0.360
H	0.079	0.066	0.05	0.180
RRMS	0.524	0.166	0.143	0.159
Methanole				
C	0.076	0.157	0.483	0.103
O	−0.511	−0.503	−0.615	−0.657
H (<i>anti</i>)	0.066	0.028	−0.045	0.088
H (<i>gauche</i>)	0.028	0.003	−0.079	0.022
H (hydroxyl)	0.314	0.311	0.335	0.422
RRMS	0.065	0.052	0.092	0.154
Formamide				
C	0.556	0.815	0.816	0.736
N	−0.634	−0.808	−0.702	−1.016
O	−0.518	−0.566	−0.583	−0.594
H (<i>trans</i>)	0.275	0.290	0.239	0.405
H (carbon)	0.238	0.326	0.287	0.457
H (<i>cis</i>)	0.024	−0.058	−0.057	0.013
RRMS	0.036	0.088	0.094	0.071
Formic acid				
H	0.021	−0.028	−0.080	0.057
C	0.748	0.831	1.023	0.682
O (carbonyl)	−0.547	−0.575	−0.637	−0.569
O	−0.591	−0.585	−0.712	−0.642
H (hydroxyl)	0.368	0.356	0.405	0.472
RRMS	0.084	0.089	0.094	0.093
Acetonitrile				
C	−0.403	−0.346	−0.169	−0.467
H	0.131	0.102	0.050	0.171
C (nitrile)	0.437	0.564	0.467	0.464
N	−0.426	−0.526	−0.448	−0.512
RRMS	0.082	0.104	0.101	0.037
Formaldehyde				
H	−0.061	−0.112	−0.132	0.040
C	0.574	0.706	0.766	0.364
O	−0.451	−0.483	−0.503	−0.443
RRMS	0.084	0.087	0.103	0.087
CO ₂				
C	0.823	0.929	1.026	0.884
O	−0.412	−0.465	−0.513	−0.442
RRMS	0.024	0.070	0.042	0.087

TABLE II.
(Continued)

Molecule ^a	Method ^b			
	AM1	PM3	MNDO	6-31G*
CO				
C	0.016	0.022	0.046	0.074
O	−0.016	−0.022	−0.046	−0.074
RRMS	0.995	0.991	0.970	0.864
H ₂ O				
O	−0.644	−0.644	−0.659	−0.808
H	0.322	0.322	0.329	0.404
RRMS	0.045	0.048	0.073	0.115
Benzene				
C	−0.091	−0.071	−0.070	−0.124
H	0.091	0.071	0.070	0.124
RRMS	0.045	0.043	0.065	0.172
Trimethylammonium				
C	−0.165	−0.1563	0.151	−0.304
N	−0.088	0.300	−0.03	0.148
H (nitrogen)	0.310	0.174	0.285	0.296
H (<i>anti</i>)	0.146	0.103	0.066	0.142
H (<i>gauche</i>)	0.140	0.118	0.061	0.166
RRMS	0.041	0.002	0.002	0.011
Nitromethane				
C	−0.181	−0.421	−0.113	−0.439
N	0.831	1.478	0.871	0.857
O	−0.492	−0.705	−0.509	−0.479
H	0.111	0.117	0.085	0.180
RRMS	0.043	0.045	0.056	0.069
Malonitrile				
C	−0.669	−0.755	−0.574	−0.304
C (nitrogen)	0.512	0.674	0.575	0.415
N	−0.405	−0.513	−0.450	−0.445
H	0.228	0.217	0.161	0.182
RRMS	0.096	0.123	0.106	0.045
SH ₂				
S	−0.451	−0.440	−0.361	−0.372
H	0.225	0.220	0.180	0.186
RRMS	0.213	0.310	0.254	0.406
Methanethiol				
C	−0.411	−0.229	0.236	−0.155
S	−0.341	−0.387	−0.369	−0.365
H (<i>anti</i>)	0.120	0.140	−0.001	0.076
H (sulfur)	0.024	0.252	0.201	0.217
H (<i>gauche</i>)	0.158	0.112	−0.034	0.152
RRMS	0.192	0.167	0.210	0.322
(CH ₃) ₂ S				
C	−0.535	−0.274	0.205	−0.321
S	−0.142	−0.202	−0.349	−0.236
H (<i>anti</i>)	0.117	0.117	0.004	0.163
H (<i>gauche</i>)	0.093	0.111	−0.013	0.138
RRMS	0.154	0.150	0.205	0.306

TABLE II.
(Continued)

Molecule ^a	Method ^b			
	AM1	PM3	MNDO	6-31G*
(CH ₃) ₂ S ₂				
C	-0.389	-0.178	0.073	-0.242
S	-0.116	-0.147	-0.125	-0.130
H (<i>anti</i>)	0.162	0.110	0.054	0.149
H (<i>gauche</i>)	0.171	0.107	0.043	0.112
RRMS	0.134	0.138	0.230	0.285
Dimethylphosphane ^d				
P	-0.350	-0.309	-0.568	-0.298
C	-0.341	-0.117	0.233	-0.185
H (<i>anti</i>)	0.150	0.075	-0.024	0.076
H (<i>gauche</i>)	0.131	0.057	0.001	0.113
H (P)	0.209	0.163	0.206	0.135
RRMS	0.257	0.396	0.253	0.495
Cyclopropylphosphane				
C(P)	0.109	0.027	0.146	0.160
C	-0.153	-0.085	-0.061	-0.268
P	-0.618	-0.376	-0.469	-0.399
H (C(P))	0.085	0.047	0.020	0.068
H (<i>syn</i>)	0.062	0.027	0.033	0.110
H (<i>anti</i>)	0.077	0.047	0.030	0.116
H (P)	0.085	0.160	0.150	0.128
RRMS	0.166	0.386	0.185	0.365
Vinylphosphane				
C (P)	-0.041	0.086	-0.019	0.115
C	-0.118	-0.312	-0.003	-0.577
H (<i>trans</i>)	0.090	0.038	0.062	0.278
H (<i>cis</i>)	0.059	-0.003	0.015	0.175
H (C(P))	0.124	0.171	0.071	0.188
P	-0.500	-0.251	-0.403	-0.777
H (P)	0.193	0.135	0.139	0.300
RRMS	0.120	0.413	0.215	0.286
Trimethylphosphane				
P	-0.485	-0.404	-0.496	-0.429
C	0.158	0.208	-0.022	0.107
C	0.111	0.208	0.022	0.160
C	0.154	0.208	0.010	0.244
H	0.011	0.022	0.065	-0.003
H	0.058	-0.031	0.061	0.008
H	-0.007	-0.031	0.060	0.001
H	0.005	-0.031	0.060	-0.014
H	0.006	-0.031	0.054	-0.009
H	0.006	-0.031	0.050	-0.029
H	0.006	-0.031	0.060	-0.031
RRMS	0.242	0.355	0.216	0.489
Phenylphosphane				
C (P)	0.036	-0.301	0.011	0.246
C	-0.079	0.030	-0.031	-0.205
C	-0.104	0.140	-0.057	-0.293
C	0.201	0.505	0.224	-0.030
C	-0.110	-0.206	-0.098	-0.060
C	0.248	-0.388	-0.228	-0.229
P	-0.522	-0.267	-0.428	-0.367

TABLE II.
(Continued)

Molecule ^a	Method ^b			
	AM1	PM3	MNDO	6-31G*
H	0.090	0.010	0.071	0.141
H	0.005	−0.105	−0.014	0.087
H	0.102	0.094	0.077	0.137
H	0.129	0.131	0.104	0.171
H	0.106	0.074	0.079	0.167
H (P)	0.197	0.141	0.145	0.118
RRMS	0.177	0.371	0.187	0.314
Phosphole				
P	−0.290	−0.112	−0.378	−0.107
C (P)	−0.071	−0.162	0.019	−0.214
C	−0.068	−0.037	−0.038	−0.086
H (P)	0.170	0.137	0.164	0.110
H (C(P))	0.124	0.131	0.070	0.176
H	0.074	0.056	0.050	0.123
RRMS	0.259	0.429	0.202	0.396

^a All structures, except phosphorous compounds, and their 6-31G* ESP charges were taken from reference 14^{32,33}.

^b For all symmetry equivalent atoms of the same type mean values are given.

^c Relative root mean square fit:

$$\text{RRMS} = \left(\frac{\sum_{i=1}^m (V_i^{\text{QM}} - V_i^{\text{CL}})^2}{\sum_{i=1}^m (V_i^{\text{QM}})^2} \right)^{1/2}.$$

^d All phosphorous compounds are 6-31G* geometries with 6-31G*(MK) ESP charges.

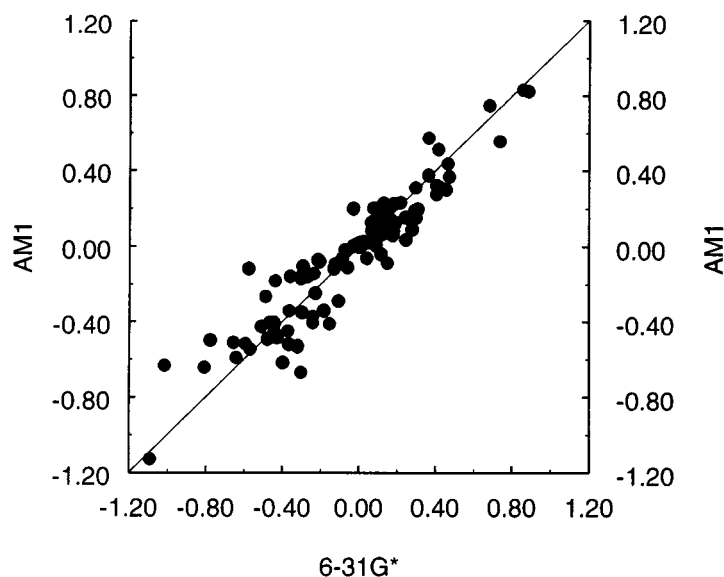


FIGURE 5. Plot of 6-31G* ESP charges against AM1 ESP charges (electronic charges). The correlation coefficient is 0.93 with a standard deviation of 0.108.

TABLE III.
Linear Fit Parameters for MEP-Derived Charges.

Dep. Variable 6-31G*	AM1	PM3	MNDO
Fits including all molecules:			
ESP corr. coeff.	0.934	0.896	0.808
Slope	0.991	0.910	0.867
SD	0.108	0.134	0.177
Coulson corr. coeff.	0.611	0.407	0.528
Slope	0.954	0.564	1.174
SD	0.238	0.275	0.255
Fits without phosphorous compounds:			
ESP corr. coeff.	0.950	0.933	0.854
Slope	1.018	0.912	0.900
SD	0.104	0.126	0.182
Coulson corr. coeff.	0.840	0.673	0.726
Slope	1.516	1.080	1.662
SD	0.187	0.237	0.239
Fits without S and P compounds:			
ESP corr. coeff.	0.960	0.940	0.888
Slope	1.070	0.905	0.926
SD	0.098	0.140	0.176
Coulson corr. coeff.	0.870	0.79	0.754
Slope	1.650	1.126	1.668
SD	0.191	0.200	0.251

convergence problems. For the 20 test compounds and using AM1 we achieved a correlation coefficient of 0.934 and a standard deviation of 0.107 with the restraint. These values are nearly identical to those obtained with our normal approach. For PM3 and MNDO the results are similar. This restraint is therefore not necessary in our “high density” ESP charge model.

Conclusions

We have demonstrated that the VESPA approach can give reasonable ESP-derived charges. In many cases it gives charges of 6-31G* quality, especially for AM1 and PM3. The speed advantage over *ab initio* methods, even those that use the fast PRISM algorithm,³⁴ is, however, substantial. The speed of the NAO-PC model for determining the electrostatic potential (and therefore avoiding any integral calculation) enables us to construct a “high density” and cost effective method. We are thus able to describe buried atoms adequately. We are also able to show that increasing the number of grid points can improve the quality of the point charges obtained, but that this does not always lead to well defined atomic charges.²⁷ However, the question as to the suitability of *ab initio* ESP

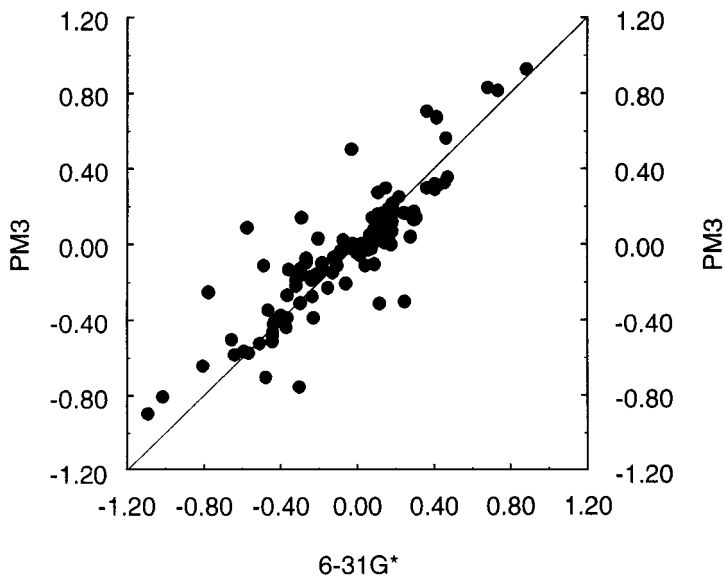


FIGURE 6. Correlation of PM3 with 6-31G* ESP derived atomic point charges (electronic charges). The correlation coefficient is 0.90 with standard deviation of 0.134.

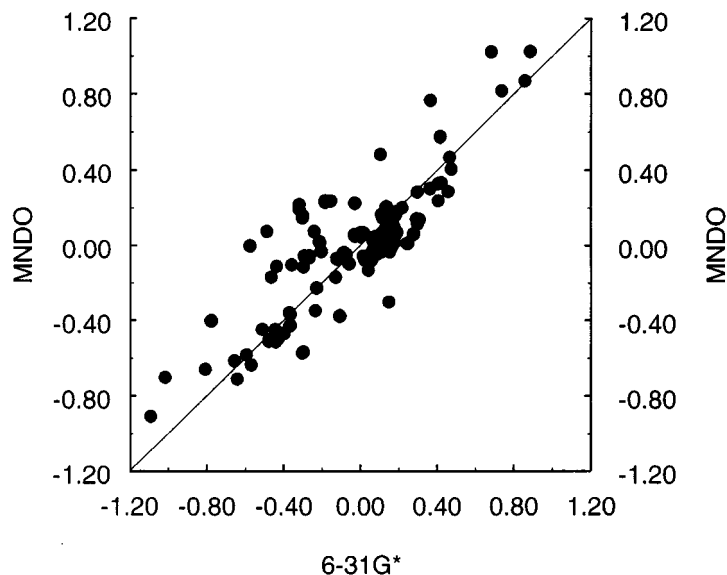


FIGURE 7. Correlation of MNDO with 6-31G* ESP derived atomic charges (electronic charges). The correlation coefficient is 0.81 with a standard deviation of 0.177.

charges as reference values remains because it is usually prohibitively expensive to calculate the electrostatic potential for such a high number of grid points around the molecule. This may result in poorly determined charges on buried atoms.

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References

1. H. Weinstein, *Int. J. Quantum Chem.*, **2**, 5969 (1975).
2. G. Pepe, D. Siri and J. P. Reboul, *J. Mol. Struct. (THEOCHEM)*, **256**, 175 (1992).
3. S. K. Burley and G. A. Petsko, *Adv. Protein Chem.*, **39**, 125 (1988).
4. M. Davis and J. A. McCammon, *Chem. Rev.*, **90**, 509 (1990).
5. S. C. Harvey, *Proteins: Struct. Func. Genet.*, **5**, 78 (1989).
6. a) J. Gasteiger and M. Marsili, *Tetrahedron*, **36**, 3219 (1990).
b) R. J. Abraham and B. Hudson, *J. Comp. Chem.*, **6**, 173 (1985).
7. C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.*, **A191**, 39 (1947).
8. R. S. Mulliken, *J. Chem. Phys.*, **23**, 1833 (1955).
9. A. J. Stone, *Chem. Phys. Lett.*, **83**, 233 (1981).
10. D. E. Williams, in *Reviews in Computational Chemistry Vol. 2*, K. B. Lipkowitz and D. B. Boyd, Ed., VCH, Weinheim, 1991, p. 219.
11. J. Tomasi, R. Bonaccorsi and R. Cammi, in *Theoretical Treatment of Large Molecules and Their Interactions*, Z. B. Maksić, Ed., Springer Verlag, Berlin, 1991, p. 230.
12. L. E. Chrilian and M. M. Francl, *J. Comp. Chem.*, **8**, 894 (1987).
13. C. M. Breneman and K. B. Wiberg, *J. Comp. Chem.*, **11**, 361 (1990).
14. B. H. Besler, K. M. Merz and P. A. Kollman, *J. Comp. Chem.*, **11**, 431 (1990).
15. G. G. Ferenczy, C. A. Reynolds and W. G. Richards, *J. Comp. Chem.*, **11**, 159 (1990).
16. M. Orozco and F. J. Lague, *J. Comp. Chem.*, **11**, 909 (1990).
17. M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, **99**, 4899 (1977).
18. J. J. P. Stewart, *J. Comp. Chem.*, **10**, 209 (1989).
19. M. J. S. Dewar, E. G. Zoebisch, E. F. Hersley and J. J. P. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985).
20. a) W. Heiden, T. Goetze and J. Brickmann, *J. Comp. Chem.*, **14**, 246 (1993). b) W. Lorensen, H. Cline, *Comp. Graph*, **21**, 163 (1987).
21. M. Marsili, in *Physical Property Prediction in Organic Chemistry*, C. Jochen, M. G. Hicks and J. Sunkel, Ed., Springer Verlag, Berlin Heidelberg, 1988, p. 249.
22. a) G. Rauhut and T. Clark, *J. Comp. Chem.*, **14** (1993) 503. b) B. Beck, G. Rauhut and T. Clark, *J. Comp. Chem.*, **15** (1994) 1064.
23. G. Rauhut, A. Alex, J. Chandrasekhar, T. Steinke, W. Sauer, B. Beck and T. Clark, VAMP V5.5, Oxford Molecular Ltd., Magdalen Centre, Oxford Science Park, Sandford-on-Thames, Oxford, OX4 4GA, England.

24. M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzales, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, *Gaussian 92*, Gaussian Inc., Pittsburgh PA, 1992.
25. R. J. Woods, M. Khalil, W. Pell, S. H. Moffat and V. H. Smith Jr., *J. Comp. Chem.*, **11**, 297 (1990).
26. M. M. Francl, C. Carey, L. E. Chrilian and D. M. Gange, *J. Comp. Chem.*, **17**, 367 (1996).
27. B. Beck, R. C. Glen and T. Clark, *J. Mol. Model. (electronic edition)*, **1**, 176 (1995).
28. D. A. Pearlman, D. A. Case, J. W. Caldwell, W. S. Ross, T. E. Cheatham III, D. M. Ferguson, G. L. Seibel, U. C. Singh, P. K. Weiner, and P. A. Kollman, AMBER 4.1, University of California, San Francisco, 1995. (available from Oxford Molecular Ltd., Magdalen Centre, Oxford Science Park, Sandford-on-Thames, Oxford, OX4 4GA, England).
29. J. A. Pople and D. L. Beveridge, *Approximate Molecular Orbital Theory*, McGraw-Hill, New York, 1970, p. 67.
30. W. Thiel, Abstracts, ACS National Meeting, Chicago, 1995.
31. C. I. Bayly, P. Cieplak, W. D. Cornell and P. A. Kollman, *J. Phys. Chem.*, **97**, 10269 (1993).
32. J. A. Pople, D. L. Beveridge and P. A. Dobosh, *J. Chem. Phys.*, **47**, 2026 (1967).
33. M. J. S. Dewar and M. L. McKee, *J. Comp. Chem.*, **4**, 84 (1983).
34. G. B. Johnson, P. M. W. Gill, J. A. Pople and D. J. Fox, *Chem. Phys. Lett.*, **206**, 239 (1993).